# HAEMOPHILUS INFLUENZAE

**Invasive Disease**

**Report Immediately**

## ✓DISEASE AND EPIDEMIOLOGY

### Clinical Description:

Invasive disease due to *H. influenzae* may produce various clinical syndromes including meningitis, bacteremia or sepsis, epiglottitis, pneumonia, septic arthritis, empyema, cellulitis, or, pericarditis; less common infections include endocarditis and osteomyelitis. Mucosal infections, such as bronchitis, sinusitis and conjunctivitis, and otitis media, can also be caused by *H. influenzae,* but they are considered to be noninvasive disease.

### Causative Agent:

*Haemophilus influenzae* is a small gram-negative coccobacillus that may be either encapsulated (types a–f) or unencapsulated (non-typeable). Non-typeable strains are thought to be less virulent than encapsulated strains. *Haemophilus influenza* type b (Hib) is the serotype that requires control measures.

BLNAR *H. influenzae* — Beta-lactamase-negative, ampicillin-resistant (BLNAR) *H. influenzae* is an emerging pathogen. The prevalence of BLNAR *H. influenzae* strains have increased in some countries (Japan and Spain), although their prevalence in the United States and elsewhere remains low (approximately 3 percent). Possible explanations for this observation include inadequate vaccination against *H. influenzae* type b in some regions, increasingly frequent use of cephalosporins, and underdosing of oral ampicillin. There are no significant differences in clinical presentation of pneumonia due to BLNAR *H. influenzae* compared to pneumonia due to ampicillin susceptible *H. influenzae* strains. These pathogens appear to have in vitro susceptibility to ceftriaxone. Depending on local susceptibility findings, ceftriaxone may be an appropriate choice for treatment of clinical infections due to BLNAR *H. influenzae* pending further study of clinical infections with this pathogen.

### Differential Diagnosis:

Invasive *H. influenzae* can cause pneumonia, bacteremia, or meningitis. The presentation of these diseases is similar to other invasive bacterial diseases such as *Streptococcal pneumoniae* or *Streptococcal pyogenes*.

### Laboratory identification:

*H. influenzae* is typically identified via culture, through blood or CSF samples. All isolates should be sent to the USL:PH for serotyping. Laboratories occasionally use antigen detection methods, but these are not considered confirmatory in the absence of culture positivity. Primary Children's Medical Center (PCMC) can test for type b. However, the test done by PCMC is a send out performed by ARUP that is an IgG antibody test. But still the isolate needs to be sent to USL:PH for serotyping.

**USL:PH:** The USL:PH serotypes all isolates of *H. influenzae* from clinical laboratories.

## Treatment (Hib):

Typical treatment regimens for Hib include cephalosporins and quinolones. Isolate the case until 24 hours after initiating appropriate antimicrobial treatment that eliminates carriage. Currently, only cefotaxime and ceftriaxone are known to eradicate Hib from the nasopharynx when they are used to treat active infection. Therefore, if the patient is treated with ampicillin or chloramphenicol instead, he/she must receive rifampin prophylaxis. Also, note that Hib disease does not necessarily confer immunity to subsequent disease. Immunize as follows:

a. Children with invasive Hib disease at <24 months of age: Immunize according to the age-appropriate schedule for unvaccinated children and as if they had received no prior doses, as disease in this age group does not reliably result in a protective immune response. Begin one month after onset of disease or as soon as possible thereafter.

b. Children with invasive Hib disease at ≥24 months of age: No Hib immunization is necessary, regardless of previous immunization status, because the disease probably induces a protective immune response and second episodes in children this age are rare. However, Hib vaccination is not contraindicated and can be given as a single antigen or as part of a combination vaccine.

## Case fatality:

Invasive infections due to *H. influenza* are serious and can be rapidly fatal. As of 2005, 15% of invasive cases were fatal in the U.S.

## Reservoir:

Humans are the only known host.

## Transmission:

*H. influenzae* infection is transmitted from person to person by droplet or direct contact with nasopharyngeal secretions of an infected person. The most common portal of entry is the nasopharynx. Newborns can become infected by inhaling amniotic fluid or genital tract secretions containing the organism.

## Susceptibility:

The vaccine only confers immunity to one strain: type b. People are uniformly susceptible to other strains of this organism. Disease before the age of 2 does not confer immunity; vaccine is still required.

## Incubation period:

The incubation period is unknown, but for invasive disease, may be as short as 2–4 days.

## Period of communicability:

If the case is not on antibiotic therapy, disease is communicable as long as organisms are present in the upper respiratory tract, which may be for a prolonged period, even without nasal discharge. If the case is on antibiotic therapy, disease is non-communicable within 24–48 hours after starting effective antibiotic therapy.

The contagious potential of invasive *H. influenzae* disease is considered to be limited. However, certain circumstances, particularly close contact with a case (e.g., in a household, daycare center, or institutional setting), can lead to outbreaks of Hib or direct secondary transmission of the disease. Asymptomatic carriage is known to occur.

## Epidemiology:

*Haemophilus influenzae* type b (Hib) is the only type for which there is a vaccine and for which control measures are considered necessary.

Before the widespread use of Hib conjugate vaccines, Hib was a leading cause of bacterial meningitis in the U.S. among children <5 years of age and a major cause of other life-threatening invasive bacterial disease in this age group. The introduction of Hib vaccine in 1988 resulted in a 99% decrease in invasive Hib disease in children younger than 5 years of age. Currently, Hib disease occurs primarily in infants too young to have completed a primary series of immunization. Secondary cases may occur in households, daycare centers, and other institutional settings.

Since the introduction of Hib vaccine, the incidence of all infection due to the encapsulated and nontypeable strains combined have decreased. However, *H. influenzae* type f has become the most common serotype causing invasive infections in the U.S. With the reduction of invasive disease due to Hib, the remaining disease is now distributed among the age groups. In Utah, invasive disease due to non-typeable strains predominates, and is seen in all age groups.

Unimmunized children, particularly those younger than four years of age, who are in prolonged close contact (such as in a household setting) with a child with invasive Hib disease are at increased risk for invasive Hib disease. Other factors causing predisposition to invasive disease include sickle cell disease, asplenia, HIV infection, certain immunodeficiency syndromes, and malignant neoplasms. In adults, underlying conditions such as chronic pulmonary disease, smoking, HIV, alcoholism, pregnancy, and older age increase the risk of *H. influenza* disease. Historically, invasive Hib was more common in boys; African American, Alaska Native, Apache and Navajo children; childcare attendees; children living in crowded conditions; and children who were not breastfed.

# ✓PUBLIC HEALTH CONTROL MEASURES

## Public health responsibility:

- Investigate all suspect cases of disease and fill out and submit appropriate disease investigation forms.

- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention.
- Identify clusters or outbreaks of this disease.
- Identify sources of exposure and stop further transmission.
- To identify the emergence of other *H. influenzae* types as causes of invasive disease.
- To monitor Hib vaccine effectiveness, and to assess progress toward disease elimination.

## Prevention:

Routine childhood vaccination is the best preventive measure against Hib disease. Good personal hygiene (which consists of proper hand-washing, disposal of used tissues, not sharing eating utensils, etc.) is also important.

## Chemoprophylaxis:

Chemoprophylaxis is ONLY indicated for contacts to Hib disease.

Indications and Guidelines for Rifampin Chemoprophylaxis for Contacts of Index Cases of Invasive Haemophilus influenzae Type b (Hib) Disease

**Chemoprophylaxis Recommended:**

Chemoprophylaxis may be indicated for household (or close) contacts of a child with invasive Hib disease, child-care or preschool contacts, and the index patient, depending upon individual circumstances as described below.

Chemoprophylaxis for index patient -

If the index patient was treated with an agent other than cefotaxime or ceftriaxone, antimicrobial therapy to eradicate nasopharyngeal carriage is recommended if either of the following also is true for the index patient:

- Is younger than two years of age, or
- Lives in a household with a child <4 years of age who has not received an age-appropriate number of doses of Hib conjugate vaccine or an immunocompromised child.

Chemoprophylaxis for household contacts -

Chemoprophylaxis is recommended for all household contacts[1] (including the index case) in the following circumstances:

- Household with at least one contact <4 years who has not received an age-appropriate number of doses of Hib conjugate vaccine[2].
- Household with a contact who is an immunocompromised child, regardless of that child's Hib immunization status

In addition to receiving antimicorbial prophylaxis, exposed unimmunized or incompletely immunized children who are household contacts of patients with invasive Hib disease must be carefully observed for signs of illness. Exposed children in whom febrile illness develops should receive prompt medical attention.

Chemoprophylaxis for child-care or preschool contacts -

Chemoprophylaxis is recommended for child-care or preschool contacts when unimmunized or incompletely immunized children attend the facility and two or more cases of Hib invasive disease have occurred among attendees within 60 days [3,4].

Exposed unimmunized or incompletely immunized children who are child care or preschool contacts of patients with invasive Hib disease must be carefully observed for signs of illness. Exposed children in whom febrile illness develops should receive prompt medical attenetion.

Recommended regimen –

- Prophylaxis should be initiated as soon as possible in contacts; in the index case it should be initiated within two weeks of the onset of disease, and may be initiated in conjuction with treatment.
- Rifampin is the drug of choice for chemoprophylaxis. The regimen is as follows – Rifampin (20mg/kg, maximum dose 600 mg) once per day for four days.
- The dose of rifampin for infants <1 month of age has not been established; some experts recommend lowering the dose to 10mg/kg.
- Consultation with an expert in infectious disease is recommended for contacts in whom rifampin is contraindicated.

**Chemoprophylaxis not recommended:**

- Chemoprophylaxis is not indicated for contacts of people with invasive disease caused by nontype b strains of *H. influenza.*
- Occupants of households with no children <4 years of age other than the index patient.
- Occupants of households when all household contacts 12 to 48 months of age have completed their Hib immunization series[5] and when all household contacts younger than 12 months of age have completed their primary series of Hib immunizations.
- For nursery school and child care contacts of 1 index case, especially people older than 2 years of age.
- For pregnant women.

1. Close contact – Close (household) contact is defined as a person who resides with the index patient or who spent ≥4 hours with the index patient for at least five of the seven days before the day of hospital admission of the index case.
2. The primary series of Hib conjugate vaccine, consists of 2-3 doses, depending on the Hib vaccine formulation. See the table 2 for more details.
3. Only children who are age-appropriately immunized and on rifampin should be permitted to enter the childcare group during the time prophylaxis is given. Children enrolling in the day care center or other setting during the time prophylaxis is given should also receive rifampin, as should supervisory personnel.
4. When a single case has occurred, the advisability of rifampin prophylaxis in exposed child care groups with unimmunized or incompletely immunized children is controversial, but many experts recommend no prophylaxis.
5. Complete immunization is defined as having had ≥1 dose of conjugate vaccine at ≥ 15 months of age; 2 doses between 12 and 14 months of age; or a 2- or 3-dose primary series (number of doses required depends on vaccine type and age at initiation) when <12 months with a booster dose at ≥12 months of age.

## Vaccine:

**Table 1** lists the Hib conjugate vaccines that are currently available in the United States. The combination vaccines that include the Hib conjugate vaccine have been licensed by the FDA following immunogenicity and safety studies. These combination vaccines decrease the number of injections needed for protection against vaccine-preventable diseases.

**Table 1**
**Comparison of conjugate vaccines against *H. influenza* type b licensed in the U.S.**

| | HbOC | PRP-OMP | PRP-T | PRP-T |
|---|---|---|---|---|
| **Commercial name** | HibTITER® | PedvaxHIB® | ActHIB®/OmniHIB® | Hiberix |
| **Manufacturer** | Wyeth | Merck | Aventis Pasteur | GlaxoSmithKline |
| **Schedule** | 2, 4, 6, 12-15 months of age | 2, 4, 12-15 months of age | 2, 4, 6, 12-15 months of age | 12-15 months |
| **Available combination** | none | Comvax (PRP-OMP-Hepatitis B) | TriHIBit® (ActHib reconstituted with Tripedia, DTaP)* Pentacel (ActHib, DTaP, and inactivated polio virus)** | none |

PRP: Polyribosylribitol phosphate; DTP: Diphtheria toxoid-Tetanus toxoid-whole cell pertussis vaccine; DTaP: Diphtheria toxoid-Tetanus toxoid-acellular pertussis vaccine.
* Indicated for use only in children ≥15 months of age.
** For use at 2, 4, 6, and 15 through 18 months of age.

**Hib Conjugate Vaccine Schedules (see Table 2 below) -** In the United States, the primary series of Hib conjuage vaccine, which is administered before seven months of age, requires two or three doses, depending upon the vaccine preparation. The minimum age for the first dose is six weeks. Hib conjugate vaccines can be administered at the same visit as other routine immunizations.

It is ideal to use the same Hib conjugate vaccine to complete the primary series. However, if it is unknown which vaccine was previously administered, or if the same vaccine is not available, the vaccines can be interchanged. If two different preparations are used, a three-dose primary series is required.

In the United States, a booster dose is required at 12 to 15 months of age (or as soon thereafter as possible); 12 months is the minimum age for the final dose. Any of the Hib conjugate vaccines may be used for the booster dose; the vaccine need not be the same as the one used for the primary series.

**Table 2**
**Recommended schedule of administration of conjugate Haemphilus influenzae vaccine**

| | **Primary series (<12 months of age)** | **Booster (≥12 months of age)** |
|---|---|---|
| Routine infant immunization | 2, 4, 6 for PRP-T and HbOC | 12 to 15 months (any Hib conjugate vaccine) |
| | 2, 4 for PRP-OMP | |
| Catch-up or lapsed immunization starting at: | | |
| <6 months of age | 3 doses, 4 to 8 weeks apart | Single dose 8 weeks from last dose for child 12 to 15 months of age |
| 7 to <12 months of age | 2 doses, 4 to 8 weeks apart up to 12 months of age | Single dose 8 weeks from last dose for child 12 months of age to 5 years |
| 12 to 14 months of age | | 2 doses, 8 weeks apart, up to 5 years of age |
| ≥15 months of age | | Single dose up to 5 years of age |

***Hib* Conjugate Vaccine Recommendations for Children Not Up-To-Date**

**"Catch-up Schedule"** – the catch up schedule for Hib conjugate vaccine depends upon the age at which the series is initiated and the number of doses previously received:

- Children <6 months of age at initiation of vaccination should receive 3 doses of the Hib conjugate vaccine at four to eight week intervals and a booster (single dose) eight weeks from the last dose for child 12 to 15 months of age.
- Children who are 7 to 11 months of age at initiation of vaccination should receive two doses of Hib conjugate vaccine at four- to eight-week intervals up to 12 months of age, and a booster (single dose) eight weeks from the last dose for child 12 months of age to 5 years.

- Children who have received ≤1 dose of Hib conjugate vaccine before 1 year of age and are now 12 to 14 months of age should receive two doses of Hib conjugate vaccine eight weeks apart, up to 5 years of age.
- Children with an incomplete series of Hib conjugate vaccination who are now 15 months to 59 months (5 years) of age should receive a single dose of Hib conjugate vaccine.

**Impaired Host Defense**
Certain children may be at increased risk of invasive Hib disease because of immune deficiency, or other host defense abnormalities (eg, sickle cell disease, functional or anatomic asplenia). These children should receive Hib conjugate vaccine as recommended for all infants. Any children younger than 59 months with these risk factors who have an incomplete vaccination history should be vaccinated according to the catch-up schedule. For unimmunized children at increased risk of Hib disease who are older than 59 months, the following is recommended:

- Unimmunized children >59 months who have sickle cell disease or asplenia should receive a single dose of Hib conjugate vaccine.
- Unimmunized children >59 months who have human immunodeficiency virus, IgG2 subclass deficiency, bone marrow transplant, or malignancy should receive two doses of Hib conjugate vaccine, separated by four to eight weeks.

Please consult the chapter on *H. influenzae* in the *Red Book* of the American Academy of Pediatrics (AAP) for a full discussion of vaccines, immunization schedules, and special circumstances. For example, children, including those >5 years of age, with underlying conditions predisposing them to Hib disease may need additional doses.

## Isolation and quarantine requirements:

**Isolation:** Cases of invasive H. influenza B disease should be isolated until 24 hours after initiating appropriate antimicrobial treatment.
**Hospital:** Standard body substance precautions.
**Quarantine:** Personal surveillance and prophylaxis with an appropriate antimicrobial when indicated by clinical situation of the contact or potential for future transmission. Otherwise, no restrictions.

# ✓CASE INVESTIGATION

## Reporting:

All cases of *H. influenzae* recovered from a sterile site.

CSTE Reporting Swimlanes

| Criterion | Reporting | |
|---|---|---|
| *Clinical Evidence* | | |
| Meningitis | N | |
| Epiglottitis | | S |

| | | |
|---|---|---|
| Healthcare record indicates a diagnosis of disease caused by *Haemophilus influenzae* | | S |
| Death certificate indicates disease caused by *Haemophilus influenzae* as a cause of death or a significant condition contributing to death. | | S |
| *Laboratory Evidence* | | |
| Isolation of *Haemophilus influenzae* (any type) from a normally sterile site | | S |
| Detection of *Haemophilus influenzae*-specific nucleic acid in a normally sterile body site using a validated polymerase chain reaction (PCR) assay | | S |
| Detection of *Haemophilus influenzae* type b (Hib) antigen in CSF | N | |

Notes:
S = This criterion alone is sufficient to identify a case for reporting.
N = All "N" criteria in the same column are necessary to identify a case for reporting.

## Case definition:

## *Haemophilus influenzae* (2015):

**Description of criteria to determine how a case should be classified.**

***Probable***

- Meningitis WITH detection of *Haemophilus influenzae* type b antigen in cerebrospinal fluid [CSF]

***Confirmed***

- Isolation of *Haemophilus influenzae* from a normally sterile body site (e.g., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid)

  OR

- Detection of *Haemophilus influenzae*-specific nucleic acid in a specimen obtained from a normally sterile body site (e.g., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid), using a validated polymerase chain reaction (PCR) assay

*Comment(s)*
Positive antigen test results from urine or serum samples are unreliable for diagnosis of *Haemophilus influenzae* disease and should not be used as a basis for case classification.

Isolates of *Haemophilus influenzae* are important for antimicrobial susceptibility testing.

**Clinical Criteria**

Invasive disease may manifest as pneumonia, bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, or purulent pericarditis; less common infections include endocarditis and osteomyelitis.

**Laboratory Criteria**

- Detection of *Haemophilus influenzae* type b antigen in cerebrospinal fluid [CSF]
- Detection of *Haemophilus influenzae*-specific nucleic acid in a specimen obtained from a normally sterile body site (e.g., blood or CSF), using a validated polymerase chain reaction (PCR) assay; or
- Isolation of *Haemophilus influenzae* from a normally sterile body site (e.g., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid)

**Epidemiologic Linkage**

Not applicable for case classification.

CSTE Case Classification Swimlanes

| | **Case Definition** | |
|---|---|---|
| **Criterion** | **Probable** | **Confirmed** |
| *Clinical Evidence* | | |
| Meningitis | N | |
| *Laboratory Evidence* | | |
| Isolation of *Haemophilus influenzae* (any type) from a normally sterile site | | S |
| Detection of *Haemophilus influenzae*-specific nucleic acid in a normally sterile body site using a validated polymerase chain reaction (PCR) assay | | S |
| Detection of *Haemophilus influenzae* type b (Hib) antigen in CSF | N | |

Notes:
S = This criterion alone is sufficient to classify a case
N = All "N" criteria in the same column are necessary to classify a case

## Case Investigation Process:

- Public health needs to immediately determine whether the reported case is due to serotype b. To do this, public health should:
  - Identify the laboratory where the initial testing occurred and
  - Phone them to ensure that the isolate is immediately sent to USL:PH for serotyping and

    - Phone USL:PH to warn them that an *H. flu* strain is coming and that serotyping needs to occur as soon as possible.
- Cases due to *Haemophilus influenzae* type b should be immediately investigated:
    - Identify all close contacts (view chemoprophylaxis section for details)
    - Assure that they are provided chemoprophylaxis and vaccine within SEVEN days of hospitalization of the index case.

## Outbreaks:

An outbreak will be defined as more than one case of Hib in a 60-day period.

## Identification of case contacts:

See Chemoprophylaxis for definition of case contacts.

## Case contact management (Hib only):

- Assure that contacts receive chemoprophylaxis. See Chemoprophylaxis for specifics.
- Ensure appropriate immunization of contacts. The number of doses required is determined by the current age of the child and the number, timing, and type of Hib vaccine doses previously received. Unvaccinated and incompletely vaccinated children <5 years of age should be scheduled for completion of the recommended age specific immunization schedule. Infants should be placed on an accelerated schedule using minimum intervals between doses. Unvaccinated high-risk individuals >5 years of age should receive 1 dose.
- Conduct surveillance. Careful observation of exposed contacts, especially children <4 years of age, is essential. Those in whom a febrile illness develops should receive prompt medical attention, regardless of Hib vaccination status.

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